

**REMARKS**

Claims 47-55, 57, 59-60, 63-79, 83-84, 86-89 and 91-98 are all the claims pending in the application. Claims 48-55, 57, 59-60, 63, 67, 69-79, 83-84, 86-89 and 92-98 are withdrawn from consideration. Claims 99 and 100 are new and withdrawn herewith. Claims 64, 66, 68, 91-93 are hereby amended. Applicants submit that support for the amendments and new claims can be found throughout the specification and do not constitute new matter, and thus entry is respectfully requested.

**I. Formal Matter**

**A. Election/Restriction Requirement**

On page 2 of the Office Action, the Office Action deems the restriction/election proper because, although it is acknowledged that the compound of formula I is not disclosed in Faye et al., Biochemistry 30:5066-5075 ("Faye"), according to the Office Action, Faye discloses libraries of fluorescently labeled GPCR ligands. The Examiner further refers to the present rejection under section 103 and states that the prior art teaches the shared technical features of the present invention.

Applicant respectfully requests that pursuant to MPEP § 821.04(a), upon allowance of the claims being examined, any claim that depends from or otherwise contains all the limitations of the allowed claims be rejoined and examined.

**B. Information Disclosure Statement**

Applicant thanks the Examiner for returning a signed and initialed copy of the PTO Form SB/08 that accompanied the Information Disclosure Statement filed February 20, 2009, and February 27, 2008, indicating consideration of the references therein.

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However, the Examiner has not considered two references listed in the February 20, 2009, PTO/SB/08 form because the dates were missing. Applicant herewith submit a new Information Disclosure Statement and revised PTO/SB/08 form with dates for the non-patent literature documents. Applicant respectfully requests that the Examiner return a signed and initialed copy of the revised PTO Form SB/08.

**C. Specification**

On page 3 of the Office Action, the Examiner indicates that the disclosure of the specification is objected to because trademark names in the application have not been capitalized and accompanied by the generic terminology.

Applicants respectfully request the withdrawal of the objections in view of the substitute specification submitted herewith, wherein the trademarks are capitalized and accompanied by the generic description.

**II. Rejection under 35 U.S.C. § 112**

On page 3 of the Office Action, the Examiner rejects claims 64, 66, 68, and 91 under 35 U.S.C. § 112, second paragraph, as being indefinite because Claims 64, 66, 68, and 91 contain the trademark/trade names BODIPY™, Cascade Blue™, and Texas Red™, which according to the Examiner renders the claim scope uncertain since the trademark or trade name cannot be used properly to identify any particular material or product.

In the interest of compacting prosecution, Applicant herewith amends Claims 64, 66, 68, and 91, to also recite the generic description of the trademarked compounds and compositions.

**III. Rejection under 35 U.S.C. § 103**

On page 5 of the Office Action, Claims 47, 64-66, 68, and 91 are rejected under 35 U.S.C. § 103(a) as being unpatentable over McCrea (Molecular Pharmacology 1996, Vol. 49, pg. 927-937)(“McCrea”) in combination with U.S. Patent 6,171,794 to Burchard (“Burchard”).

The Office Action states that McCrea teaches salmeterol, which is a ligand for  $\beta_1$ - and  $\beta_2$ -adrenoceptors and further teaches that cells containing stimulated  $\beta_1$ - and  $\beta_2$ -adrenoceptors accumulate cAMP, which is measured by stimulating C6 cell monolayers with salmeterol and measuring the conversion of radiolabeled adenine (8- $^3\text{H}$ Adenine) into  $^3\text{H}$ cAMP. The Office Action acknowledges that McCrea fails to teach a fluorescently tagged salmeterol. However, the Office Action states that Burchard teaches labeling nucleotide analogues with the fluorescent label BODIPY630/650. Thus, the Office Action concludes that one would have been motivated to label McCrea’s salmeterol with Burchard’s fluorescent label BODIPY-630/650 because Burchard teaches that fluorescent labels are preferred to other types of labeling including radioactive isotopes, and further that one would have had a reasonable expectation of success to label McCrea’s salmeterol with Burchard’s fluorescent label BODIPY-630/650 because techniques for labeling nucleotide analogues are well established in the art as evidenced by Burchard.

Applicant respectfully traverses the obviousness rejection for the reasons set forth below.

Initially, Applicant notes that the factual inquiries which must precede a legal conclusion on obviousness are the determination of (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) objective evidence of nonobviousness, such as commercial success, long-felt but unsolved needs which the invention has satisfied, failure of others to make the claimed invention,

copying of the alleged invention, and unexpected results brought about by the invention.

Furthermore, when determining the patentability of a claimed invention which combines two known elements (or rather which combines the teaches of prior art references), a pertinent question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *Akamai Technologies Inc. v. Cable & Wireless Internet Services Inc.*, 68 USPQ2d 1186 (Fed. Cir. 2003). Particularly, it is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007).

Neither McCrea nor Burchard, alone or in combination, discloses or suggests monitoring GPCR ligand binding of any kind, nor any labeling of GPCR ligands, in living cells or in any other form. McCrea investigated duration of agonist action at beta adrenoceptors, by culturing cells in radiolabelled adenine, exposing cells to agonists, washing at set time intervals, and then performing cell lysis and analyzing for intracellular levels of radiolabelled cAMP. The emphasis of the McCrea is the duration of the cyclic AMP response to salmeterol after washing the salmeterol away. McCrea fails to teach or suggest the location of the receptors in the cell at which salmeterol is binding. Therefore, one of ordinary skill in the art would not have been motivated to look to the BODIPY™ labeling because the focus of the study in McCrea was relating to the beta-adrenoceptors, namely their identity and susceptibility to agonists and antagonists, not for the purpose of measuring cAMP.

Burchard fails to cure the deficiencies of McCrea. Burchard is directed to distinguishing nucleic acid sequences by their hybridization properties with nucleic acid probes. Burchard discloses labeling the target polynucleotide sequence in a sample, applying an immobilized

probe or probes to the sample under hybridization conditions, and washing off and removing any polynucleotide sequences which are not hybridized or bound to the probe or probes. The amount of labeled polynucleotide remaining can then be measured (see column 4, lines 1-5, lines 44-49; and column 9, lines 12-17). However, Burchard fails to disclose ligand binding for GPCR receptors. Rather, Burchard discloses BODIPY™ labeling of polynucleotide, not the particular challenges associated with attaching a fluorophore in such a way as to retain pharmacological activity in view of the fact that the ligand binding site for GPCR receptors is usually deep within the transmembrane regions of the receptor. Contrary to the Examiner's assertions, it would not have been *prima facie* obvious to employ a label such as BODIPY™ in "a GPCR ligand, inhibitor, or intracellular enzyme or a substrate or inhibitor of a drug transporter", as claimed by the Applicant.

Furthermore, the claimed invention is not a mere recitation of salmeterol plus BODIPY, rather, Applicant's claimed invention is related to a compound of formula I, such a formula being neither disclosed nor suggested anywhere in the cited prior art. Indeed, Applicant's disclosure emphasizes the importance of the design of the compound, the tag having a specific influence on the pharmacology of the resulting product (see page 5, lines 23-27 of the specification).

Furthermore, neither McCrea et al nor Burchard discloses or suggests the capability of carrying out its respective disclosed method *in vivo*. Burchard performs its method on samples of polynucleotides, to which immobilized probes are applied so that the unhybridized polynucleotides can subsequently be washed away. The assay used by McCrea relies on lysis of the cells and therefore it provides no teaching concerned with the use of monitoring salmeterol binding in living cells. There is no teaching in McCrea of visualizing the location of beta

adrenoceptors by culturing the cells in fluorescent media such as GFP (green fluorescent protein) together with fluorescent salmeterol, and imaging the green fluorescent cell surface (outlined by GFP fluorescence) and the contrasting red or blue fluorescent agonist bound to beta adrenoceptors. Nor is there teaching of introducing antagonists and determining the change in visualization of adrenoceptors.

Accordingly, Applicants submit that neither McCrea nor Burchard teaches the concept of visualizing whole cells without lysis to determine information. In fact, McCrea teaches away from the present invention by concentrating on lysis of cells and investigating cell contents. Moreover, Burchard further teaches away by looking at nucleic acid molecules, and not at cells or cell contents.

Finally, as disclosed in Figures 1 and 2, Applicants have obtained unexpectedly accurate and detailed results, with very precise visualization of cell surface receptors, which show a precise overlay of cell surface and receptor sites. Applicants have shown that by incorporating a linker in the claimed fluorescently tagged (ant)agonists, the receptor binding is not affected or influenced by the presence of the bulky fluorescent component. This result was not expected and has not previously been demonstrated.

**V. Double Patenting**

On page 7 of the Office Action, the Examiner provisionally rejects Claims 47, 64-66, 68, and 91 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 21-24 of co-pending Application No. 11/576,035. Since the double patenting

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rejection is provisional, Applicant defers addressing the merits of the provisional rejection until one of the cited pending Applications issues in accordance with MPEP § 804(I)(B).<sup>2</sup>

**Conclusion**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The U.S. Patent and Trademark Office is hereby directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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<sup>2</sup> Deferral of addressing the merits of the rejection is clearly contemplated by MPEP § 804(I)(B), which states that a “provisional” double patenting rejection is designed simply to make Applicants aware of a potential problem. Thus, no response on the merits is required because no patented claims are available to be analyzed.